**APOE-ε2 allele associated with higher prevalence of sporadic Parkinson disease**

Xuemei Huang, MD, PhD; Peter C. Chen, BS; and Charles Poole, MPH, ScD

**Abstract**—Background: The link of the apolipoprotein (APOE) -ε4 allele to Alzheimer disease (AD) has led to studies investigating the role of apoE polymorphisms in Parkinson disease (PD). The authors hypothesized that any association between PD and APOE alleles and genotypes would be too small to be detected or precisely estimated by an individual case-controlled study. Method: The hypothesis was tested by systematic review and meta-analysis of results from case-control studies that provided clear clinical or pathologic criteria for PD and that reported APOE genotype frequencies. Published reports were obtained from MEDLINE, Biosis Previews, and ISI Web of Science searches, supplemented by citation analysis from retrieved articles. The authors estimated and compared prevalence odds ratios (OR) for PD in relation to each allele and genotype. Results: Twenty-two eligible studies were identified. There was no evidence of heterogeneity (p > 0.4) or publication bias (p > 0.2) for any allele or genotype. The estimated summary OR for one or more copies of each APOE allele was 1.20 for APOE-ε2 (95% CI, 1.02 to 1.42), 0.83 for APOE-ε3 (95% CI, 0.63 to 1.09), and 0.99 for APOE-ε4 (95% CI, 0.87 to 1.14). Conclusions: Unlike Alzheimer disease, for which the APOE-ε4 allele increases the prevalence and the APOE-ε2 allele is protective, the authors’ analysis shows the APOE-ε2 allele, but not the APOE-ε4 allele, to be positively associated with sporadic Parkinson disease.

**Methods. Source of data.** We searched MEDLINE (PubMed), Biosis Previews, and ISI Web of Science databases for English language publications from January 1, 1966 to June 24, 2003 using the key words “Parkinson” and “apoE” or “apolipoprotein.” The search revealed 125 publications. Additional information was found by following the reference citations from retrieved articles. Two a priori inclusion criteria were 1) case-control studies in which the cases were defined as either clinically diagnosed or pathologically confirmed PD; and 2) information on genotype frequency was either contained in the article or obtainable from the original investigators. If the authors reported results in more than one publication, we used only the one with more comprehensive data. The following information was extracted (see table E-1 on the Neurology Web site) from each included study: sample size; APOE genotype; age and gender ratio of the subjects; the year of publication; and the country in which the study was conducted. Some desirable information was not available in most of these articles, including ethnicity of subjects, age at onset, clinical subtypes, and pathologic characteristics.

**Statistical analysis.** Funnel plots of log case-control odds ratios (OR), a log-rank test, and the regression test were examined for evidence of publication bias. Overall homogeneity test p values were computed for the Cochran Q statistic.

**ORs for APOE alleles were calculated by contrasting persons who have at least one copy of the specified allele with those persons who have no copies. These analyses were conducted with and without adjustment for confounding among alleles. The adjusted analyses used the Mantel–Haenszel OR estimator to adjust, for
example, for APOE-ε3 and APOE-ε4 to estimate the association between PD and the APOE-ε2 allele. “Dose-response” analyses were also conducted using a 0, 1, 2 scale for each allele, without adjustment for the other alleles. Because the results of the unadjusted analyses conformed closely to those of the dose-response analyses, the latter are not reported. ORs of APOE genotypes were estimated by contrasting persons with specific genotypes (e.g., the APOE-ε2ε3 allelic configuration). In these analyses, persons with two copies of the APOE-ε3 allele, the most common configuration, were placed into the reference category.

To explore associations between characteristics of studies and their results, we performed stratified and meta-regression analyses. The dependent variable was the log OR, and the independent variables were the study characteristics. The meta-regressions were fit using random effects, inverse variance-weighted linear regression, with the among-studies variance estimated by restricted maximum likelihood.13 The log OR was transformed back to the original ratio scale; the meta-regression coefficient estimates the ratio of the average OR in studies with one characteristic to the average OR with another characteristic. The following study characteristics were examined with cutoff points for binary variable specifications selected to achieve as close as possible to balanced distributions: year of publication (1996 or before, after 1996), geographic locale (Europe, Asia, and North America), average age of study participants (≤67 years, >67 years), and gender (50% male, >50% male).

We also conducted a χ² test of Hardy–Weinberg equilibrium (on 5 df) in the control group for each study. The test results created two natural groups of studies for stratified and meta-regression analysis: one group including three studies had p ≤ 0.1, suggesting that the source populations were not in Hardy–Weinberg equilibrium, and the other group including the remainder of the studies had p ≥ 0.4.14,15 Given little or no evidence of publication bias, overall heterogeneity, or appreciable associations between study results and study characteristics, fixed effects summary OR estimates and 95% CIs were computed. We used the 95% confidence limit ratio (CLR), the ratio of the upper to lower 95% confidence limits, to gauge the precision of the summary estimates. All analyses were conducted using STATA versions 7 and 8 software (Stata, Inc., College Station, TX).

Results. We identified 31 articles that met the first selection criterion; 21 of these articles reported complete genotype frequency information, whereas the remaining 10 reported only allele frequencies. After request, authors of 1 of these 10 articles provided genotype frequencies.16 Consequently, our analysis is based on results from 22 independent studies whose attributes are listed in table E-1 (see table E-1 on the Neurology Web site), reflecting 2,157 patients and 7,831 control subjects. The APOE allele counts from the studies that could not be included are given in table E-2 (see table E-2 on the Neurology Web site).

Neither visual inspection of funnel plots (figure 1) nor the tests of funnel plot symmetry gave any indication of publication bias (i.e., all p values from the log-rank test11 and the regression test12 were acceptably high; table). There was also little or no evidence of overall heterogeneity (p ≥ 0.8 in all instances; see table). Regarding the alleles of a priori interest, the APOE-ε4 allele showed no association with sporadic PD in the available literature as a whole (see figure 2, figure 3, and the table), whereas the APOE-ε2 allele had a positive association with sporadic PD.

There was a suggestion of an inverse association between the APOE-ε3 allele and sporadic PD (see figure 2

### Table: Meta-analysis results for APOE alleles and genotypes in sporadic Parkinson’s disease

<table>
<thead>
<tr>
<th>APOE Measure</th>
<th>Alleles*</th>
<th>Genotypes†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ε2</td>
<td>ε3</td>
</tr>
<tr>
<td>Homogeneity P</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Begg P</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Egger P</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Summary OR</td>
<td>1.20</td>
<td>0.83</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.02–1.42)</td>
<td>(0.63–1.09)</td>
</tr>
<tr>
<td>95% CLR</td>
<td>1.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* The odds ratios for the APOE alleles contrast persons who have at least one copy of the specified allele with persons who have no copies, unadjusted within studies for the other two alleles. For adjusted odds ratios, please refer to the text in the results section.
† The odds ratios for APOE genotypes contrast persons who have specified genotypes with persons who have ε3ε3 alleles—the most common form of APOE genotypes.
and the table), but this association was less precise than those for the other two alleles, owing to the extremely high frequency of the APOE-ε3 allele (with 95% of control subjects having at least one copy of the APOE-ε3 allele in all studies combined). Moreover, whereas the results did not change in the allele-adjusted analyses for APOE-ε2 (adjusted OR = 1.21; 95% CI, 1.02 to 1.45) or APOE-ε4 (adjusted OR = 0.98; 95% CI, 0.85 to 1.14), the adjustment for APOE-ε2 and APOE-ε4 shifted the association between APOE-ε3 and sporadic PD to the null value (adjusted OR = 1.01; 95% CI, 0.62 to 1.64). This change suggests that the unadjusted estimate for APOE-ε3 was confounded downward because of the inverse association of this allele with another allele (APOE-ε2) that has a positive association with sporadic PD. In the analysis of specific genotypes (see table) in which interallelic confounding cannot occur, the APOE-ε2ε4 configuration emerged as the only genotype markedly associated with sporadic PD, although a trend toward a positive association with APOE-ε2ε3 was seen.

Year of publication, percentage of male participants, and average age were not associated with the OR estimates from the individual studies for any of the three alleles. For APOE-ε2, but not APOE-ε3 or APOE-ε4, there was a suggestion of a somewhat stronger positive association in studies done in Europe than elsewhere. Using only the 14 European studies, the summary estimate for the APOE-ε2 allele was OR = 1.28 (95% CI, 1.06 to 1.54; homogeneity p = 0.07). After deletion of the three studies with evidence among the control subjects that the source populations were not in Hardy–Weinberg equilibrium, the positive association with APOE-ε2 also became slightly stronger, OR = 1.23 (95% CI, 1.04 to 1.46; homogeneity p = 0.8), than in all studies combined.

**Discussion.** We estimated a positive association between the APOE-ε2 allele and sporadic PD and little or no association with APOE-ε3 or APOE-ε4 alleles, especially after adjusting for mutual confounding among the three alleles. The association seems to be specific for the APOE-ε2 allele because increased prevalence of sporadic PD appeared to be associated with the APOE-ε2ε4 (and possibly the APOE-ε2ε3) genotypes, although such an association seems weaker for persons with the APOE-ε2ε3 genotype. The APOE-ε2ε2 genotype is rare in the covered populations (0.64% of control subjects), thus leading to the lowest precision in OR estimation. More research including special populations (if there are any) is needed to obtain a reasonably precise estimate of the association between sporadic PD and this uncommon genotype.

As noted, one-third of the reports could not be included because only allele counts were reported. Nevertheless, we note that seven of these nine studies reported that the APOE-ε2 allele was more frequent among patients with PD than among control subjects (see table E-2 on the Neurology Web site).

Our findings of the association of APOE-ε2 (not APOE-ε4) with increased prevalence of PD underscore a major pathophysiologic difference among neurodegenerative diseases such as PD and AD, often perceived as "similar" age-related disorders. In the past, consistent with their roles in AD, the APOE-ε2 and APOE-ε3 alleles have been demonstrated to facilitate neurite outgrowth, accumulate in neurons, and inhibit apoptosis, whereas the APOE-ε4 allele is less efficient in these regards. A process unrelated to apoE actions in neuronal repair and remodeling may also hold the clue for understanding its involvement in PD. There is evidence that other polymorphisms (e.g., N-acetyltransferase 2, monoamine oxidase B, glutathione transferase 1, and those on mitochondria tRNAglu) may be associated with sporadic PD, underscoring the need to include the interplay of apoE and environmental factors to understand this sporadic disease.

In the past, almost every reported association of gene polymorphism and PD has been contradicted by other studies. This includes the association of APOE-ε4 with different PD subgroups (such as PD dementia or familial PD) and with age at onset.

The present study demonstrates that the existing

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  Neurology 2004;62:2333–2334

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